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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/584,586	05/31/2000	Brian Sorrentino	1340-1-021CIP	4632

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/584,586	Applicant(s) SORRENTINO ET AL.	
	Examiner Anne Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-28* is/are pending in the application.

4a) Of the above claim(s) *16-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed June 21, 2002 (Paper No. 15) has been entered. Claim 4 has been amended. Claim 2 has been cancelled.

Accordingly, Claims 1 and 3-28 remain pending in the instant application.

Claims 16-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

This application contains claims 16-28 drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, Claims 1 and 3-15 are examined herein.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, and 13-15 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 3-5 of the Office Action of Paper No. 11 (mailed 3/28/02), because the specification, while being enabling for a method of performing *ex vivo* expansion of (a) a **murine** HSC comprising transducing the murine HSC with a nucleic acid encoding an ABC transporter and (b) a

human HSC comprising transducing the human HSC with an ABC transporter and expanding the cell population for a period up to 3 days, does not reasonably provide enablement for a method of *ex vivo* expansion of an HSC by transducing the HSC with an ABC transporter-encoding nucleic acid using any vector, and culturing the gene-modified HSC for more than 3 days, to thereby expand the cell population. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At pages 3-4 of the response, Applicants argue that non-human primate HSCs can be transduced with retroviral vectors at low frequencies. Applicants point to Dunbar et al. (1996) and Tisdale et al. (1998). However, the Examiner has not received the Dunbar reference. The Examiner cannot comment on evidence not of record. The Tisdale reference is post-filing art (published August 15, 1998) and therefore the skilled artisan would not have had the benefit of the teachings of Tisdale at the time the instant invention was made. The instand Application claims priority to May 28, 1998. Therefore, enablement must be judged as of May 28, 1998. In response to Applicants arguments, that non-human primate HSCs can be transduced with retroviral vectors, it is noted that the claims require much more than successful transduction, as the claims also require *ex vivo* expansion of the transduced cells. For reasons of record, this has been a notable problem in the art, a problem to which researchers have directed intensive effort with limited success.

At page 4, paragraph 1 of the response, Applicants assert that "human stem cells" (not hematopoietic stem cells) "can be transduced with vectors at a low frequency and recent studies have shown that transduction rates of up to fifteen percent can be achieved in human patients." However, Applicants have offered no evidence in support of this assertion and an Attorney's assertions cannot take the place of evidence. Furthermore, the Examiner cannot evaluate this assertion because it is unclear if the results are the subject of post-filing art or prior art. Moreover, it is unclear from Applicants' statement whether the stem cells are hematopoietic stem cells or another type of stem cell. Furthermore, a scope of

enablement has already been indicated. The indicated scope acknowledges that both human and murine HSCs can be successfully transduced, using appropriate vectors.

At page 4, paragraph 2 of the response, Applicants assert that the success of the claimed invention does not depend on a high transduction frequency. Again, no support is offered for this assertion. Applicants reason that even if a low but detectable portion of stem cells are transduced, it is the ABC transporter-mediated expansion of these cells which allows for amplification and expansion. However, the prior art demonstrates expansion of a human HSC transduced with an ABC transporter for a period of only 3 days. Neither the prior art nor the instant specification demonstrate expansion beyond 3 days. Furthermore, the instant specification does not provide specific guidance for expanding the transduced cells beyond 3 days. In an art that is unpredictable, the specification must provide specific guidance.

Furthermore, Applicants arguments are not commensurate in scope with the scope of the claimed invention. All claims require *ex vivo* expansion of the transduced HSC cells. All claims cover prolonged expansion in culture, but the specification is not enabling for expansion beyond 3 days. Furthermore, Claim 15 specifically recites expansion for at least 9 days. For reasons of record, the specification is not enabling for expansion beyond 3 days.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 3-12, and 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by McDonagh et al. (WO 93/24613), for reasons of record advanced on pages 6-7 of the Office Action of Paper No. 11 (mailed 3/28/02).

Claims 1, 3-12, and 14 stand rejected under 35 U.S.C. 102(e) as being anticipated by McDonagh et al. (US Pat. No. 5,837,536), for reasons of record advanced on pages 6-7 of the Office Action of Paper No. 11 (mailed 3/28/02).

At page 7, paragraph 2 of the response, Applicants assert that the Examiner's suggestion that McDonagh et al. teach an ex vivo expansion of HSCs is not an accurate representation of the teachings of McDonagh et al. because the expansion of cells in McDonagh et al simply reflects the effects of hematopoietic cytokines on committed progenitor cells and does not require the MDR1 vector or reflect an expansion of true repopulating cells. Applicants seem to be arguing limitations that are not in the claims. Moreover, Applicants have not pointed to anything which suggests that the limitations of the claims are not fully met by the teachings of McDonagh. Applicants point to McDonagh at Column 15, line 31, which clearly states that the cells were expanded 10-fold. This does not support Applicants argument. Applicants go on to argue that expansion of gene modified HSCs would not have occurred in this example because, according to Applicants, the retroviral promoter used to express the MDR1 gene in the G1MD11 AA1.2 vector (a promoter derived from the Moloney Murine Leukemia Virus) does not promote expression in primitive cells. Applicants conclude that "[a]s a result, **expansion of HSC's would not occur** because there would be no expression of the ABC transporter (MDR1) in the primitive

stem cells" (original emphasis). Applicants are wrong. Expansion of HSCs did occur. See McDonagh et al. at Column 15, line 31 which states that during *in vitro* culture "the cells expand approximately 10 fold."

At page 7, paragraph 3 of the response, Applicants assert that, while the McDonagh et al. patent does mention the use of a Harvey-based MDR1 vector at Column 3, line 66, as well as the use of other promoters, e.g. Column 4, lines 44-55, there is no teaching that HSCs modified to express an ABC transporter could be preferentially expanded *ex vivo*. However, McDonagh et al. **did** teach that HSCs expressing an ABC transporter were expanded 10 fold *in vitro*. See Example 4. Applicants conclude that McDonagh et al. does not provide sufficient detail to enable one of skill in the art to make and use the present invention. On the contrary, McDonagh et al. did teach, make, and use the claimed invention. See Example 4. For reasons of record, the teachings provided by McDonagh et al. meet each and every claim limitation.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER